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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/072,436	02/05/2002	Ursula Markau	1803-332-999	3877

24341 7590 04/08/2003

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EXAMINER

HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/072,436

Applicant(s)

MARKAU ET AL.

Examiner

Richard G Hutson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 February 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-23 is/are pending in the application.
- 4a) Of the above claim(s) 1-4 and 18-23 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 5-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 2/5/2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other:

DETAILED ACTION

Claims 1-23 are still at issue and are present for examination.

Election/Restrictions

Applicant's election of Group II, Claims 5-17 in Paper No. 4 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-4 and 18-23 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

Applicants statements on the first line of the specification to state that this application claims priority to European Patent Application No. 97121151.1, filed December 2, 1997, is acknowledged. **It is noted that a certified copy of the priority document has not been received.**

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the

list may not be incorporated into the specification but must be submitted in a separate paper."

Specification

The disclosure is objected to because of the following informalities:

It is noted that throughout the application applicants recite "SEQ ID **NO**: 6" (page 14, line 1), "SEQ ID **No**. 10" (page 6, line 17) "SEQ ID **No**. 2" (page 13, line 15), "SEQ ID **NO**. 5" (page 13, line 27) and "SEQ ID **No.**: 10" (page 9, line 5). It is suggested that applicants maintain consistency through out the application when referring to a sequence identifier (i.e. SEQ ID NO:).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 (6-17 dependent on) is indefinite in that it is unclear when a modified DNA polymerase becomes a modified form of a DNA polymerase other than a DNA polymerase from *Carboxydotherrnus hydrogenoformans*.

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-7, 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 5-7, 10 and 11 are directed to all DNA sequences encoding a modified DNA polymerase that is a modified form of a DNA polymerase obtainable from *Carboxydotherrnus hydrogenoformans*, wherein said modified polymerase (a) exhibits reverse transcriptase activity in the presence of magnesium ions and/or manganese ions; (b) has reduced or no 5'-3' exonuclease activity; and © has substantially no RNase H activity and vectors comprising said DNA polymerase.

The specification, however, only provides a single representative species, having the amino acid sequence of SEQ ID NO: 11, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these enzymes by any identifying structural characteristics or properties other than the activities recited in claims 5, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full,

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clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 5-7, 10 and 11 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA sequence encoding a modified DNA polymerase that is a modified form of a DNA polymerase obtainable from *Carboxydotherrnus hydrogenoformans*, wherein said DNA sequence comprises the nucleotide sequence of SEQ ID NO: 10, does not reasonably provide enablement for any DNA sequence encoding any modified DNA polymerase that is a modified form of a DNA polymerase obtainable from *Carboxydotherrnus hydrogenoformans*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in

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the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 5-7, 10 and 11 are so broad as to encompass any DNA sequence encoding any modified DNA polymerase that is a modified form of a DNA polymerase obtainable from *Carboxydotherrnus hydrogenoformans*, wherein said modified polymerase (a) exhibits reverse transcriptase activity in the presence of magnesium ions and/or manganese ions; (b) has reduced or no 5'-3' exonuclease activity; and (c) has substantially no RNase H activity and vectors comprising said DNA sequence. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of DNA sequences encoding any modified DNA polymerase, broadly encompassed by the claims. The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the claimed DNA sequences nor on the encoded DNA polymerases. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to that DNA sequence encoding a modified DNA polymerase that is a modified form of a DNA polymerase obtainable from *Carboxydotherrnus*

hydrogenoformans, wherein said DNA sequence comprises the nucleotide sequence of SEQ ID NO: 10.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any DNA sequence encoding any modified DNA polymerase that is a modified form of a DNA polymerase obtainable from *Carboxydotherrnus hydrogenofomans*, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting polymerase, reverse transcriptase, 5'-3' exonuclease and RNase H activity; (B) the general tolerance of such modified DNA polymerases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of any DNA polymerase obtainable from *Carboxydotherrnus hydrogenofomans* with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation

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that would be required to determine which substitutions would be acceptable to retain the activities claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those DNA sequences of the claimed genus encoding DNA polymerases with the claimed activities.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any DNA sequence which encodes any number of amino acid modifications of any DNA polymerase obtainable from *Carboxydotherrmus hydrogenoformans*. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 15-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention of claims 15-17 appears to employ a novel vector, pdelta 2-225AR₄, (claims 15-17) and a novel strain of *E. coli* GA1 (claim 17). Since the vector and strain are essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. Neither the vector nor the organism are fully disclosed, nor have they been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the vector pdelta 2-225AR₄, (claims 15-17) and the novel strain of *E. coli*, GA1.

It is noted that applicants have deposited the organism but there is no indication in the specification as to public availability. If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

1. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request;

2. all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
3. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and
4. the deposit will be replaced if it should ever become inviable.

Remarks

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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A handwritten signature in black ink, appearing to read 'R. Hutson', with a horizontal line extending from the end of the signature.

Richard Hutson, Ph.D.

Patent Examiner

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April 4, 2003